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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

In re Application of	
Application Number: 07-975750	Filed: Nov 13-92
Art Unit	Examiner

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Paper No. 18

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1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:

United States Patent Application Publication No. 6,777,401, page _____, line _____,

United States Patent Number _____, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which designates the United States, WIPO Pub. No. _____, page _____, line _____.

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2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

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9-4-02
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Unit: _____

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(12) **United States Patent**
Ullrich et al.

(10) **Patent No.: US 6,177,401 B1**
(45) **Date of Patent: Jan. 23, 2001**

(54) **USE OF ORGANIC COMPOUNDS FOR THE INHIBITION OF FLK-1 MEDIATED VASCULOGENESIS AND ANGIOGENESIS**

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(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **08/193,829**

(22) Filed: **Feb. 9, 1994**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/038,596, filed on Mar. 26, 1993, now abandoned, which is a continuation-in-part of application No. 07/975,750, filed on Nov. 13, 1992, now abandoned.

(51) **Int. Cl.**[7] **A61K 31/00**

(52) **U.S. Cl.** **514/1**; 435/7.2; 436/501; 530/350; 530/399

(58) **Field of Search** 536/23.5; 435/69.1, 435/172.1, 240.2, 252.3, 320.1, 325, 361, 7.2; 424/93.2; 514/44, 1; 935/32, 57, 70, 71; 436/501; 530/399, 350

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,185,438	2/1993	Lemishka .
5,712,395	1/1998	App et al. .
5,763,441	6/1998	App et al. .
5,766,860	6/1998	Terman et al. .
5,792,771	8/1998	App et al. .
5,792,783	8/1998	Tang et al. .
5,869,742	2/1999	Köster et al. .

FOREIGN PATENT DOCUMENTS

WO 92/03459	3/1992	(WO) .
WO 92/14748	9/1992	(WO) .
WO 92/17486	10/1992	(WO) .
WO 94/10202	5/1994	(WO) .
WO 95/21868	8/1995	(WO) .
WO 96/20403	7/1996	(WO) .

OTHER PUBLICATIONS

S.H. Orkin Et Al., "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy", Dec. 7, 1995.*

H. Ueno et al.., Science 252:844–848, May 10, 1991.*

H. Ueno et al.., J. Biol. Chem. 267(3):1470–1476, Jan. 25, 1992.*

L.A. Tartaglia et al., J. Biol. Chem. 267(7), 4304–4307, Mar. 5, 1992.*

Risau et al., 1988, "Changes in the Vascular Extracellular Matrix During Embryonic Vasculogenesis and Angiogenesis," *Development Biology 125*:441–450.

Ferrara et al., 1989, "Pituitary Follicular Cells Secrete a Novel Heparin–Binding Growth Factor Specific for Vascular Endothelial Cells," *Biochem. Biophys. Res. Comm. 161*:851–858.

Gospodarowicz et al., 1989, "Isolation and Characterization of a Vascular Endothelial Cell Mitogen Produced by Pituitary–Derived Folliculo Stellate Cells," *Proc. Natl. Acad. Sci. USA 86*:7311–7315.

Leung et al., 1989, "Vascular Endothelial Growth Factor Is a Secreted Angiogenic Mitogen," *Science 246*:1306–1309.

Conn et al., 1990, "Purification of a Glycoprotein Vascular Endothelial Cell Mitogen From a Rat Glioma–derived Cell Line," *Proc. Natl. Acad. Sci. USA 87*:1323–1327.

Ullrich et al., 1990, "Signal transduction by receptors with tyrosine kinase activity", *Cell 61*:203–212.

Ferrara et al., 1991, "The Vascular Endothelial Growth Factor Family of Polypeptides," *J. Cell Biochem. 47*:211–218.

Kashles et al., 1991, "A Dominant Negative Mutation Suppresses the Function of Normal Epidermal Growth Factor Receptors by Heterodimerization," *Mol. Cell. Biol. 11*:1454–1463.

Klagsburn et al., 1991, "Regulators of Angiogenesis" *Annu. Rev. Physiol. 53*:217–39.

Maglione et al., 1991, "Isolation of Human Placental cDNA Coding For a Protein Related to the Vascular Permeability Factor," *Proc. Natl. Acad. Sci. USA 88*:9267–9271.

Matthews et al., 1991, "A Receptor Tyrosine Kinase cDNA Isolated From a Population of Enriched Primative Hematopoietic Cells and Exhibiting Close Genetic Linkage to c–kit," *Proc. Natl. Acad. Sci. USA 88*:9026–9030.

Mitchell et al., 1991, "Recombinant Expression and Characterization of the 121 Amino Acid Form of Vascular Endothelial Growth Factor (VEGF)," *J. Cell. Biochem., Keystone Symposia on Molecular and Cellular Biology*, Supplement 15C, Excerpt G207.

(List continued on next page.)

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(57) **ABSTRACT**

The present invention relates to the use of proteins, peptides and organic molecules capable of modulating Flk-1 receptor signal transduction in order to inhibit or promote angiogenesis and vasculogenesis. The invention is based, in part, on the demonstration that Flk-1 tyrosine kinase receptor expression is associated with endothelial cells and the identification of vascular endothelial growth factor (VEGF) as the high affinity ligand of Flk-1. These results indicate a major role for Flk-1 in the signaling system during vasculogenesis and angiogenesis. Engineering of host cells that express Flk-1 and the uses of expressed Flk-1 to evaluate and screen for drugs and analogs of VEGF involved in Flk-1 modulation by either agonist or antagonist activities is described.

The invention also relates to the use of FLK-1 ligands, including VEGF agonists and antagonists, in the treatment of disorders, including cancer, by modulating vasculogenesis and angiogenesis.

16 Claims, 25 Drawing Sheets